CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-341

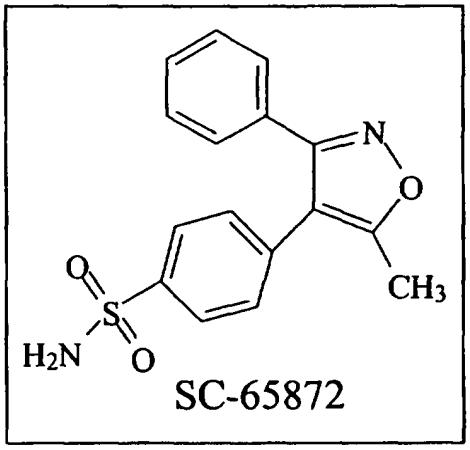
PHARMACOLOGY REVIEW

Exhibit A

DIVISION OF ANTI-INFLAMMATORY, ANALGESIC AND OPHTHALMOLOGIC DRUG PRODUCTS (HFD-550)

PHARMACOLOGY AND TOXICOLOGY REVIEW

NDA	**21-341**
DRUG:	Bextra; Valdecoxib; SC-65872
SPONSOR:	Pharmacia G.D. Searle LLC 4901 Searle Parkway Skokie, IL 60077
SUBMISSION DATE:	January 15, 2001
TYPE OF SUBMISSION:	Original [505 (b)(1)]
DATE COMPLETED:	October 11, 2001
REVIEWER:	W. C. Josie Yang, DVM, Ph.D.
CDER STAMP DATE:	January 16, 2001
DATE RECEIVED IN HFD-550:	January 17, 2001
DATE ASSIGNED TO REVIEWER:	January 19, 2001
USER FEE DUE DATE:	November 16, 2001
DRUG CATEGORY:	NSAID, Cyclooxygenase 2 (COX-2) Inhibitor
FORMULA:	4-(5-Methyl-3-phenyl-4-isoxazolyl)benzenesulfonamide; $C_{16}H_{14}N_2O_3S$; MW=314.36



SC-65872

INGREDIENTS	QUANTITIES (MG)			Function
	10 mg	20 mg	40 mg	
Valdecoxib	10.0	20.0	40.0	Active Ingredient
Lactose Monohydrate, NF				
Microcrystalline Cellulose, NF				
Pregelatinized Starch, NF				
Croscarmellose Sodium, NF				
Magnesium Stearate, NF				
Purified Water, USP				

CAS Nº: 181695-72-7

INDICATION: Prevention and Treatment of Acute Pain in Adults; Treatment of Primary Dysmenorrhea; Relief of Signs and Symptoms of Osteoarthritis and Adult Rheumatoid Arthritis

DOSAGE FORM: 5 mg, 10 mg, 20 mg and 40 mg film coated tablets.

RELATED DRUG/INDs/NDAs/DMFs:

KEY WORDS: SC-65872; Valdecoxib, COX-2; NSAID

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1. PHARMACOLOGY

1.1. OVERVIEW

The actions of currently available marketed NSAIDs to inhibit the production of prostaglandins (PGs) by cyclooxygenases (COX) can be divided into three groups:

- modification of the enzymes by acetylation of a serine residue at the active site, such as aspirin thus resulting in an irreversible inhibition of COX activity;
- induction of time-dependent irreversible inhibition of enzymes, such as indomethacin or flurbiprofen; and
- induction of reversible competitive inhibition, such as ibuprofen and mefenamate.

The common side effects shared by NSAIDs are as followings:

- GI ulceration and intolerance,
- inhibition of platelet aggregation via blockade of thromboxane (TBX) synthesis,
- inhibition of uterine motility resulting in prolongation of gestation,
- inhibition of PG-mediated renal function, and
- hypersensitivity reactions.

Two distinct COX enzymes, COX-1 and COX-2, were identified recently. COX-1, a constitutively expressed form, displays in blood, vessels, gut and kidney that produce PGs which are required for normal physiological functions. COX-2, an inducible isoenzyme, is encoded by a different gene from COX-1 and only exists in high concentrations under the inflammatory condition induced by cytokines or inflammatory mediators or following mitogenic stimulation. COX-1 mRNA could be detected in all tissues with highest expressed levels found in platelets, vascular endothelial cells, liver, stomach, spleen, kidney collecting tubules and colon. In contrast, COX-2 mRNA levels were extremely low in all normal tissues except rat brain. Both enzymes have approximately 60% homology and are able to convert arachidonic acid to PGH_2 with similar affinity. The amino acid residues thought to be essential for this enzymatic conversion are conserved in both structures.

It has been postulated that NSAID-induced GI toxicity is caused by the inhibition of PGs which were mainly regulated by COX-1 in the GI tract and required for normal physiological function. Most currently available NSAIDs inhibit the COX-1 and COX-2 nonselectively or have preferential selectivity for COX-1 except two recently approved NSAIDs, celecoxib and rofecoxib. The action of mechanism of action of celecoxib and rofecoxib is believed due the inhibition of prostaglandin synthesis mainly through the inhibition of cyclooxygenase-2 (COX-2). At therapeutic concentrations in humans, both celecoxib and rofecoxib do not inhibit the cyclooxygenase-1 (COX-1) isoenzyme.

Valdecoxib (SC-65872 - $C_{16}H_{14}N_2O_3S$), a highly selective cyclooxygenase-2 (COX-2) inhibitor, is a diarylsubstituted isoxazole compound and proposed for the following indications: management of acute pain in adults, treatment of primary dysmenorrhea, and relief of signs and symptoms of osteoarthritis and adult rheumatoid arthritis.

1.2. PHARMACODYNAMIC EFFECTS RELATING TO PROPOSED INDICATIONS

Study Type	Species/Indicator	Treatment/Route	Dose	Findings
ANTI-INFLAMMATORY/ANALGESIC ACTIVITIES				
Effects on Adjuvant-Induced Arthritis	♂ Lewis Rats 10/group	po bid for 10 days (6-8 hr apart)	Valdecoxib: 0-3 mg/kg/day; Parecoxib: 0-0.3 mg/kg/day; SC-66905: 0-10 mg/kg/day	Dose-related inhibition of adjuvant- induced arthritis with ED_{50} values: Valdecoxib - 0.036 mg/kg/day; Parecoxib - 0.078 mg/kg/day; SC-66905 - 1.68 mg/kg/day.
Effects on Carrageenan-Induced Inflammatory (Hargreaves Model) Hyperalgesia, Edema, and PGE_2 Production	♂ SD Rats 5-10/group	po single dose	Valdecoxib: 0, 30 mg/kg	↓ hyperalgesia by 81% at 3 hr post-dose; ↓PGE_2 by 81% in paw exudate at 2 hr post-dose.
	♂ SD Rats 5/group			↓ hyperalgesia, paw edema, PGE_2 in paw exudate, and PGE_2 in CSF by 62%, 63%, 74%, and 86%, respectively.
	♂ SD Rats 5/group	po single dose	Valdecoxib: 0, 30 mg/kg Naloxone: 0.5 mg/kg sc	Valdecoxib blocked carrageenan-induced hyperalgesic pain; subcutaneous administration of Naloxone at 0.5 mg/kg did not alter the analgesic action of Valdecoxib.
	♂ SD Rats 5-8/group	po single dose	Valdecoxib: 0, 1, 3, 10, 30, 50, and 100 mg/kg	Dose-dependent ↓ of hyperalgesia and paw edema with ED_{50}'s (mg/kg): Hyperalgesia / Edema — Valdecoxib 13.7 / 5.9; SC-66905 1.5 / 1.06
	♂ SD Rats 5/group	po single dose	valdecoxib: 0, 5, 30 mg/kg	↓ hyperalgesia and paw edema at 30 mg/kg. Hyperalgesia / Edema — Single Dose ↓91% / ↓67%; Repeated Dose ↓100% / ↓69%
		bid for 8-day	Valdecoxib: 2.5, 15 mg/kg bid	
	♂ Lewis Rats 4-13/group	po single dose	valdecoxib: 0, 0.03, 0.3, 10 mg/kg	↓ PGE_2 in CSF to undetectable levels at 1 and 3 hr postdose with 10 mg/kg; ↓ PGE_2 levels in paw exudate by 43% and 57% 4 hr after dosing with 0.03 and 0.3 mg/kg, respectively.
		bid for 7-day	0.5 mg/kg	↓ PGE_2 levels in CSF to normal levels at 24 hr post 1st dose.
	♂ SD Rats 2-4/group	intrathecal single dose	valdecoxib: 0, 30, 100, 300 μg	≥100 μg: ↓ hyperalgesia, paw edema, and PGE_2 in paw exudate and CSF
	♂ SD Rats 5/group	iv or po single dose	valdecoxib: 0, 50, 200 μg	↔
Effects on Hyperalgesia and Allodynia in Post-Surgical Pain Model	♂ SD Rats 6/group	po single dose	valdecoxib: 0, 3, 10, 30, and 100 mg/kg	Dose-dependent reduction of tactile allodynia and thermal hyperalgesia.
		iv single dose		
ANTI-PYRETIC ACTIVITY				
Effect on LPS-Induced Fever in Dogs	♀ Beagle Dogs 4/group	po single dose	Valdecoxib: 0, 0.5, 5 mg/kg	Blocked LPS-induced fever at 5 mg/kg.

1.2.1. REFERENCES

1.2.1.1.1. Valdecoxib, SC-66905 and Parecoxib: Effect on Adjuvant-Induced Arthritis in [redacted] Rats; Date: 01-Feb-2000, Document No. BRD96D1796a. (Vol. 1.13)

1.2.1.1.2. Valdecoxib Inhibits Hyperalgesia and Allodynia in Rat Model of Post-Operative Pain; Date: 16-Feb-2000, Document No. BRD99D1997. (Vol. 1.13)

1.2.1.1.3. Effect of Valdecoxib on Edema, Hyperalgesia and Prostaglandin Production in the Rat Carrageenan Model; Date: 28-Jan-2000, Document No. BRD99D1991. (Vol. 1.13)

1.2.1.1.4. Effect of Valdecoxib (SC-65872) on PGE_2 Levels in Cerebrospinal Fluid and Paw Exudates/Synovial Fluid in Rat Adjuvant Arthritis; Date: 26-Jan-2000, Document No. BRD98D1917. (Vol. 1.13)

1.2.1.1.5. Distribution of Valdecoxib (SC-65872): Into the Central Nervous System in the Rat; Date: 20-Jan-2000, Document No. BRD98D1930. (Vol. 1.13)

1.2.1.1.6. Valdecoxib (SC-65872): Inhibitory Activity on Fever, Cyclooxygenase-1 and Cyclooxygenase-2 in Dogs; Date: 13-Jan-2000, Document No. BRD98D1901. (Vol. 1.13)

1.2.1.1.7. Effect of Naloxone on the Analgesic Activity of Valdecoxib (SC-65872); Date: 25-Jan-2000, Document No. BRD98D1911. (Vol. 1.13)

1.2.1.1.8. Effect of Intrathecal Administration of Valdecoxib (SC-65872) on Hyperalgesia, Edema and PGE_2 Production in Hargreaves Model; Date: 01-Feb-2000, Document No. BRD98D1916. (Vol. 1.13)

1.2.1.1.9. Valdecoxib Rapidly Reverses Inflammatory Hyperalgesia and Prostaglandin E_2 Production; Date: 01-Feb-2000, Document No. BRD98D1928. (Vol. 1.13)

1.2.1.1.10. Evaluation of Valdecoxib and SC-66905, COX-2 Inhibitors, as an Anti-Inflammatory and Analgesic Agent; Date: 20-Apr-2000,Document No. BRD98D1929a. (Vol. 1.13)

1.2.1.1.11. Evaluation of Single Vs. Chronic Administration of Valdecoxib (SC-65872) on Hyperalgesia and Edema; Date: 26-Jan-2000, Document No. BRD99D1931. (Vol. 1.13)

1.3. General and Mechanism Related Pharmacodynamics

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